REMARKS

Claims 1, 4, 9, 101 and 110-114 are pending. Claim 1 is amended to incorporate matter from claims 110 and 113 in the alternative. No claims are added or canceled.

The present invention concerns compositions that modulate gene expression via an RNA interference pathway. In particular, the compositions comprise (i) a first oligonucleotide and (ii) a second oligonucleotide which are not covalently linked but are at least partially complementary to each other. The compositions further comprise a conjugate group on at least one of the first and second oligonucleotides. Such compounds are useful in a number of therapeutic, diagnostic, and research applications involving gene silencing.

Applicants respectfully request reconsideration of the rejections of record in view of the foregoing amendments and the following remarks.

Priority

Applicants disagree with the Examiner's assertions concerning the pending claims right of priority to application 08/870,608 ("the 608 application"). According to the M.P.E.P., "the fundamental factual inquiry [underlying the written description requirement] is whether the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the invention as now claimed.[1] The M.P.E.P. further states that the "subject matter of the claim need not be described literally (i.e., using the same terms or *in haec verba*) in order for the disclosure to satisfy the description requirement."[2] And to make a determination regarding the adequacy of the disclosure, the entire specification must be considered.[3] If the specification of the 608 application *as a whole* were considered by one skilled in the art, it would be readily apparent that applicants were in possession of the compositions recited in the claims as amended herein at the time the 608 application was filed.

Basis for amended claim 1 is summarized as follows Claim 79 of the 08/870608 application states that "at least one of said first and said second oligonucleotides have portions

[1] M.P.E.P. § 2163.02 (quoting *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555 (Fed, Cir. 1991)).
[2] *Id.*
[3] M.P.E.P. § 2163, II, A, (2).

flanking said central portions having chemical modifications which make them resistant to single-stranded nucleases and increase their affinity for the other oligonucleotide of the duplex." This disclosure is supplemented on pages 21-24 of the filed specification of the 08/870608 application where such chemical modification are described and include 2'-OCH_3 and phosphorothioate linkages.

Basis for the claims is discussed in more detail in the following paragraphs. In making the rejection, the Examiner asserts that in the 608 application "only in claims 78-80 and in examples 27-29 are double stranded RNA oligomers taught" (Office Action at page 4). The Examiner further alleges that in the rest of the 608 application "the specification and claims are drawn to single stranded RNA oligomers" (*Id*). Applicants note, however, that claim 79 of the 608 application, which the Examiner acknowledges is directed to double stranded oligomers, recites "chemical modifications which make them resistant to single-stranded nucleases and increase their affinity for the other oligonucleotide of the duplex substituents which increase affinity or resistance." One such modification, recited in claim 80 of the 608 application, is the inclusion of a 2'-methoxy substituent on the double stranded construct. Importantly, the recitation of "chemical modifications which make them resistant to single-stranded nucleases and increase their affinity for the other oligonucleotide of the duplex substituents which increase affinity or resistance" provides a clear link to the remaining description in the specification that refers to such modifications.

In light of the above discussion, Applicants submit that Example 27-a of the 608 specification describes duplexes that comprise a "sense strand" and an "antisense strand,"[4] and refers to the strands of the duplexes as "oligoribonucleotides."[5] Original claims 78, 79, and 80 of the 608 specification also recite double-stranded RNAs that comprise a duplex of "a first oligonucleotide and a second oligonucleotide" and have various chemical modifications. The description provided in the 608 specification thus demonstrates that applicants were in possession of duplexes comprising first and second strands, in which the strands are referred to as "oligoribonucleotides" or "oligonucleotides," and are chemically modified.

[4] 608 specification as originally filed at page 92.
[5] 608 specification as originally filed at example 27-b, page 96; and example 28, at page 99.

Moreover, since the term "oligoribonucleotides" is used in Example 27-a to refer to molecules that are part of a duplex, and the term "oligonucleotides" is used in original claims 78, 79, and 80 to refer to molecules that are also double-stranded, any description in the 608 specification using these terms relates to compounds that are single stranded or part of a duplex. Once the entirety of the 608 specification is so considered, it becomes apparent that the presently claimed complementary first and second oligonucleotides are fully supported by the 608 application, in view of the abundant description of various "oligoribonucleotides" and "oligonucleotides" provided in the specification.

In this regard, with respect to the specific features recited in the claims as amended herein, the 608 application specification describes oligonucleotides bound to conjugate groups.[6]

The specification of the 608 application also describes oligonucleotides of the length recited in claim 4. Specifically, the 608 specification expressly indicates that oligoribonuelcotides and oligoribonucleosides can be any of a variety of lengths. For example, the specification states that:

> Preferred oligoribonucleotides and oligoribonucleosides in accordance with this invention preferably comprise from about 5 to about 50 nucleoside subunits. In the context of this invention it is understood that this encompasses non-naturally occurring oligomers as hereinbefore described, having 5 to 50 nucleoside subunits. It is more preferred that the oligoribonucleotides and oligoribonucleosides of the present invention comprise from about 15 to about 25 nucleoside subunits.[7]

In addition, Example 27-a describes particular, double-stranded oligonucleotides in which each of the oligonucleotides present in the duplexes is 17 or 20 nucleotides in length. The 608 specification thus describes duplexes comprising oligoribonucleotides having various lengths, and specifically describes oligoribonucleotides having 17 to 25 nucleoside subunits.

Moreover, the 608 specification also includes copious description of oligoribonucleotides and oligonucleotides having regions of any of a variety of chemical modifications, such as 2'-O-CH_3 modifications:

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[6] 608 specification as originally filed at page 26, lines 12 to 16.
[7] 608 specification as originally filed at page 24, lines 5 to 13.

> In certain preferred oligomeric compounds of the invention, the first or first and third segments of oligomeric compounds are formed of nucleoside subunits that include 2'-substituent groups thereon. In preferred embodiments, the 2'-substituent group includes…C_1-C_{20} alkoxy…Preferred alkoxy substituents include methoxy…[8]

The 608 application also describes oligonucleotides in which such chemical modifications "are located at one or both of the 3' or the 5' termini of the oligomeric compounds. In certain preferred compounds there are from one to about eight nucleoside subunits that are substituted with such substituent groups."[9]

The specification of the 608 application further describes oligonucleotides having modified internucleoside linkages:

> Other preferred oligomeric compounds of the invention include oligoribonucleotides having nucleoside subunits connected by phosphorus linkages including phosphorothioate, 3'-(or 5') deoxy-3' (or 5') thio-phosphorothioate, phosphorodithioate, phosphoroselenate, 3'- (or 5') deoxy phosphinate, borono phosphate, 3'-(or 5') deoxy-3' (or 5') amino phosphoramidate, hydrogen phosphonate, borono phosphate ester, phophoramidate, alkyl or alryl phosphonate, and phosphotriester."[10]

In addition, the "oligoribonucleotides" in the double-stranded compounds described in Examples 27-a, 27-b, and 28 of the 608 application comprise various combinations of phosphorothioate and 2'-O-CH_3 modifications, and these examples indicate that the chemical modifications to the strands of the duplexes impart increased stability to exonucleases.[11] The experimental examples of the 608 specification thus describe duplexes comprising sense and antisense oligoribonucleotides that comprise combinations of chemical modifications, such as 2'-O-CH_3 and phosphorothioate linkages, that confer nuclease resistance.

Significantly, the 608 specification makes clear that the described chemical modifications are suitable, and even desirable, for double-stranded compounds. For instance, Example 27-a explains that certain chemical modifications make duplexes "more stable to

[8] 608 specification as originally filed at page 8, lines 4 to 10.
[9] 608 specification as originally filed at page 10, lines 1 to 11.
[10] 608 specification as originally filed at page 8, lines 22 to 30.
[11] 608 specification as originally filed at page 92, lines 25-33; and page 99, lines 10-17.

exonuclease digestion,"[12] and the 608 specification indicates that chemical modifications that improve the nuclease resistance of an oligonucleotide are advantageous for double-stranded compounds.[13]

The specification of the 608 application, when properly considered in its entirety, therefore provides support for the presently claimed oligonucleotide duplexes, and the present application is therefore entitled to the benefit of the June 6, 1997 filing date of the 608 application.

Alleged Obviousness

Claims 1, 4, 9, 101, and 110-114 were rejected under 35 U.S.C. § 103(a) as allegedly rendered obvious by U.S. patent application publication number US 2004/0259247 ("the Tuschl application") in view of U.S. patent application publication number US 2004/0054155 ("the Wolf application"), Schwarz, *et al.*, *Molecular Cell*, 2002, 10, 537-548 ("the Schwarz article"), and Manoharan, M., Marcel Dekker, New York, 2001, 391-467 ("the Manoharan chapter"). Applicants respectfully request reconsideration and withdrawal of this rejection because, as discussed above, the present claims are entitled to the benefit of the filing date of the 608 application, which is June 6, 1997. Since this date is before the priority date of the Tuschl and Woolf applications and the publication dates of the Schwarz article and the Manoharan chapter, these references are not available as prior art with respect to the subject application. Withdrawal of the rejection is respectfully requested.

[12] 608 specification as originally filed page 92, lines 25-30; see also page 99, lines 10-17 (describing desirability of stabilized modified oligoribonucleotides in a duplex).
[13] 608 specification as originally filed at, e.g., page 21, lines 16 to 19.

Closing

The foregoing is believed to constitute a complete and full response to the Office Action of record. Accordingly, an early and favorable reconsideration of the rejections and an allowance of all of pending claims is earnestly solicited.

Respectfully submitted,

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